What is the effect of dietary cholesterol intake on risk of cardiovascular disease?

Conclusion

Moderate evidence from epidemiologic studies relates dietary cholesterol intake to clinical cardiovascular disease (CVD) end-points. Many randomized clinical trials on dietary cholesterol use eggs as the dietary source. Independent of other dietary factors, evidence suggests that consumption of one egg per day is not associated with risk of coronary heart disease or stroke in healthy adults, although consumption of more than seven eggs per week has been associated with increased risk. An important distinction is that among individuals with type 2 diabetes, increased dietary cholesterol intake is associated with CVD risk.

Grade: Moderate

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here.

Evidence Summary Overview

The Nutrition Evidence Library (NEL) systematic review identified 16 studies published since 1999 that evaluated the effect of dietary cholesterol intake on cardiovascular disease (CVD) risk conducted in the US, Europe, Mexico and Japan. These studies focused on dietary cholesterol, in the absence of dietary saturated fat. Eight randomized controlled trials (RCTs), including two methodologically strong studies (Ballesteros, 2004; Knopp, 2003) and six methodologically neutral studies (Goodrow, 2006; Greene, 2005; Harman, 2008; Mutungi, 2008; Reaven, 2001; Tannock, 2005) with sample size ranging from 28 to 201 subjects were reviewed. Five prospective cohort studies, including four methodologically strong studies (Djousse, 2008; Hu, 1999; Qureshi, 2007; Tanasescu, 2004) and one methodologically neutral study (Nakamura, 2006) ranging in size from 5,687 to 80,082 subjects, were reviewed. One meta-analysis of 17 studies was methodologically strong (Weggemans, 2001), and two systematic reviews, one methodologically strong pooled analysis of 167 cholesterol feeding studies in 3,519 subjects (McNamara, 2000) and one methodologically neutral review of eight prospective cohort studies on dietary cholesterol and six prospective cohort studies on eggs (Kritchevsky and Kritchevsky, 2000) met the eligibility criteria and were reviewed. The majority of these articles reported on comparisons of egg vs. egg substitute or no egg intake. In studies comparing eggs vs. egg substitute, one randomized controlled trial (Ballesteros, 2004) and one pooled analysis (McNamara, 2000) showed that low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol increased in hyper-responders, but did not change in hypo-responders; overall, the LDL:HDL did not change in hypo- or hyper-responders. Identification of hypo-and hyper-responders showed inter-individual variation to dietary cholesterol that may result in differing health outcomes for individuals with different genetic predispositions.

Harman et al, (2008) found that LDL-C decreased in both egg and egg substitute groups and two studies in elderly adults (Greene, 2005; Goodrow, 2006) indicated that LDL-C and HDL-C were not affected by egg intake. Two RCTs showed an increase in LDL-C diameter in the egg group (Ballesteros, 2004; Greene, 2005). Two RCTs in 65 insulin-sensitive and 75 insulin-resistant subjects determined that egg consumption was associated with increased LDL-C, but only in insulin -sensitive subjects (Knopp, 2003; Tannock, 2005). However, Reaven et al, (2001) found that high cholesterol intake did not increase LDL-C in either insulin-sensitive or insulin -resistant sub-groups. All studies that measured HDL-C found that HDL-C was increased with egg consumption, and one such study was in a carbohydrate (CHO)-restricted diet background (Mutungi, 2008). One study assessed markers of inflammation and found increased C-reactive protein (CRP) and serum amyloid A with high egg consumption, but found no difference in circulating cytokines (Tannock, 2005). One meta-analysis of 17 studies indicated that high dietary cholesterol intake increased the total cholesterol (TC):HDL-C ratio. However, this effect was attenuated in the low saturated fatty acid (SFA) subgroup (Weggemans, 2001).

In the prospective cohort studies, Djousse et al, (2001) found that egg consumption up to six eggs per week in the Physicians' Health Study was not associated with risk of all-cause mortality, but consumption of more than seven eggs per week was associated with a 23% increased risk of death. In the Japan Public Health Center study, egg consumption was not associated with coronary heart disease (CHD) incidence (Nakamura, 2006). In Nutrition and Health Examination Examination Survey I (NHANES I), no relationship was established between egg consumption (more than six eggs per week) and risk of stroke or ischemic stroke, and risk of myocardial infarction (MI) and all-cause mortality was not different between egg and non -egg consumption groups (Qureshi, 2007). A combined analysis of the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), found no significant (NS) association between egg consumption and risk of CHD or stroke in men or women (Hu, 1999). A review of epidemiological studies (Kritchevsky and Kritchevsky, 2000) showed there was no association between consumption of one egg per day and risk of cardiovascular disease (CVD), but only in non-diabetic men and women. Furthermore, three methodologically strong prospective cohort studies warned that egg consumption was associated with increased CVD risk in subjects with type 2 diabetes (T2D) (Djousse, 2001; Hu, 1999; Tanasescu, 2004) and this warrants further investigation.

Evidence Summary Paragraphs

Ballesteros et al, 2004 (positive quality) This was a randomized crossover trial conducted in Mexico to evaluate the effects of dietary cholesterol provided by whole eggs on plasma lipids and LDL-C atherogenicity in a pediatric population. Children were divided into two groups and randomly assigned to either the egg or egg substitute intervention for 30 days followed by a three-week washout period, followed by the opposite intervention for 30 days. The children consumed either two whole eggs (providing 518 mg additional dietary cholesterol) or the equivalent amount of egg whites with added color, served scrambled for breakfast in the school cafeteria. On weekends, eggs and egg substitute were packed for consumption and parents were instructed on proper administration. Sixty children [30 boys (aged 10.6±1.6 years) and 30 girls (aged 10.2±1.5 years)] were enrolled in the study; 54 children (25 boys and 29 girls) completed the trial. Children were classified as hyporesponders (N=36), defined as no increase or <0.05 mmol/L increase in plasma cholesterol for 100mg cholesterol, or hyperresponders (N=18), defined as an increase of >0.06mmol/L in plasma cholesterol for 100mg cholesterol. During the egg consumption period, the hyperresponders had an elevation of both LDL-C (from 1.54±0.38 to 1.93±0.36mmol/L) and HDL-C (from 1.23±0.26 to 1.35±0.29mmol/L), while hyporesponders had NS alterations in plasma LDL-C or HDL-C. All subjects, however, had an increase in LDL peak diameter (P<0.01) and a decrease in the smaller LDL sub-fractions (P<0.01) during the egg consumption period.

Djousse et al, 2008 (positive quality) This was a prospective cohort study (a component of the Physicians' Health Study) conducted in the US to examine the association between egg consumption and the risk of CVD and mortality. Information on egg consumption was obtained at baseline, 24, 48, 72, 96 and 120 months using a semi-quantitative food frequency questionnaire (FFQ). A total of 21,327 American male physicians (mean age 53.7±9.5 years, range 40-85 years) were included in the analysis. After an average follow-up of 20 years, a total of 1,550 new MI, 1,342 incident strokes and 5,169 deaths occurred in the cohort. Egg consumption was not associated with incident MI, total stroke or types of stroke. While egg consumption of up to six eggs per week was not associated with the risk of all-cause mortality, consumption of seven or more eggs per week was associated with a 23% increased risk of death after controlling for confounders (P for trend<0.0001). In addition, compared with the lowest category of egg consumption, intake of seven or more per week was associated with 22% increased risk of death in the absence of prevalent diabetes whereas a two-fold increased risk of death was observed in the presence of prevalent diabetes (P for interaction between diabetes and egg consumption was 0.029 in the parsimonious model and 0.09 in the multivariable adjusted model).

Goodrow et al, 2006 (neutral quality) This was a randomized crossover trial conducted in the US to investigate the effects of egg consumption on serum concentrations of lutein, zeaxanthin, lipids and lipoprotein cholesterol in older adults. The 18-week trial consisted of four phases: Phase I (baseline period in which participants were instructed to limit their consumption of foods high in lutein and zeaxanthin and to avoid eggs or high-egg content foods), phase II (five-week intervention during which subjects consumed either no egg or egg substitute or one egg per day in addition to their normal diet), phase III (four-week washout period similar to phase I), and phase IV (five-week crossover intervention from phase II). A seven-day diet record was obtained from each subject during each phase of the study. Thirty-three subjects [seven men (mean age 77±4 years) and 26 women (mean age 81±2 years)] were enrolled and completed the trial. After the egg consumption period, serum lutein increased by 26% and serum zeaxanthin increased by 38% (both P<0.001), while serum concentrations of TC, LDL-C, HDL-C and triglycerides (TG) were not affected.

Greene et al, 2005 (neutral quality) This was a randomized crossover trial conducted in the US to evaluate the effects of a cholesterol challenge on plasma cholesterol, LDL size and LDL susceptibility to oxidation in the elderly. Subjects were assigned to either the equivalent of three eggs per day (containing approximately 640 mg of dietary cholesterol) or the same volume of egg substitute for 30 days, followed by a three-week washout period, and then assigned to the opposite intervention for 30 days. A seven-day dietary record was collected during each period. Forty-two older adults (13 men over 60 years of age, 29 postmenopausal women, no age specified) enrolled and completed the trial. In both men and women, TC (P<0.05), LDL-C (P<0.05), HDL-C (P<0.001) and LDL particle size (P<0.05) increased during the egg consumption period. However, there were no differences between egg and egg substitute consumption periods with regard to LDL:HDL ratio, plasma TGs, apo-B concentration and the parameters of LDL oxidation.

Harman et al, 2008 (neutral quality) This was an RCT conducted in the United Kingdom to compare the combined effects of two energy-restricted diets, with and without added dietary cholesterol (two eggs per day) on weight loss, plasma lipids, and lipoproteins. Fifty-three subjects were randomly assigned to one of two parallel dietary interventions: An energy restricted diet (reduced by 500-1,000kcal per day) which included two eggs (N=27) or no eggs (N=26) per day for 12 weeks. All subjects received dietetic counseling and an individualized diet plan, and weight loss was monitored through regular meetings with a dietitian. A seven-day food diary was completed at baseline and after six weeks. Forty-five subjects completed the trial, 24 in the group consuming eggs (eight male, 17 female, mean age 44.9±8.4 years) and 21 in the control group (six male, 15 female, mean age 43.0±10.5 years). Energy intake fell by 25 and 29% in the egg-fed and non-egg-fed groups, resulting in a moderate weight loss of 3.4 kg (P<0.05) and 4.4kg (P<0.05), respectively. The concentration of plasma LDL-C decreased in the non-egg-fed group after six weeks (P<0.01) and in the egg-fed and non-egg-fed at 12 weeks relative to baseline, however, there were no other significant changes in plasma lipoproteins or LDL particle size.

Hu et al, 1999 (positive quality) This was an analysis of two prospective cohort studies, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), to examine the effect of egg consumption on CVD outcomes in men and women. A total of 37,851 men (aged 40-75 years) and 80,082 women (aged 34-59 years) were followed for incident nonfatal MI, fatal CHD and stroke. Dietary intake of eggs was determined by validated FFQ. There were 866 cases of CHD and 258 cases of stroke in men during the 8-year follow-up, and 939 cases of CHD and 563 cases of stroke in women during the 14-year follow-up. After adjustment for age and other CHD risk factors, there was NS association between egg consumption and risk of CHD or stroke in men or women. The relative risk (RR) of CHD across categories of intake was 1.08 (P for trend=0.75) for the highest egg consumption group (more than one egg per day) for men, and 0.82 (P for trend=0.95) for women. However, when sub-groups were analyzed, there was a significant association between egg intake and risk of CHD in subjects with T2D (RR=2.02, P for trend=0.04, for men and RR=1.49, P for trend=0.008, for women), which warrants further investigation.

Knopp et al, 2003 (positive quality) This was a randomized crossover trial to determine if insulin resistance influences the serum lipoprotein response to dietary cholesterol and SFA. Specifically, this was a double-blinded, randomized, three-period crossover clinical trial with three four-week intervention periods with four-week washout. Subjects were divided based on body mass index (BMI) and insulin sensitivity to three groups: Insulin sensitive (IS, N=65); insulin resistant (IR, N=75; and obese insulin-resistant (OIR, N=58). The intervention was consumption of zero, two or four eggs per day with a background National Cholesterol Education Program (NCEP) Step 1 diet (monitored by three-day food records). Consumption of four eggs per day was associated with an increase in LDL-C in the IS (increased 7.8%) and IR (increased 3.3%) groups (both P<0.05), but not the OIR group (NS). However, HDL-C levels also increased significantly in all groups: 8.8%, 5.2%, and 3.6% in IS, IR and OIR groups, respectively. Additionally, there were significantly decreased TG levels (-5.5%) with consumption of four eggs per day in the IS group. A limitation of this study was that the IR and OIR groups had significantly higher LDL-C at baseline than the IS group.

Kritchevsky and Kritchevsky 2000 (neutral quality) This was a semi-systematic review of epidemiological studies that examine the relationship between dietary cholesterol and heart disease risk. The summary of epidemiological evidence relating dietary cholesterol to CVD risk covered eight prospective cohort studies from 1981-1999. When the full-range of confounding factors including dietary fat and fiber were taken into account, the association between dietary cholesterol and heart disease risk was small (6% increased risk for 200mg per 1,000kcal per day difference in cholesterol intake). The summary of epidemiological evidence relating egg consumption to CVD risk covered six prospective cohort studies. Taking into account dietary confounding factors, there was no association between egg consumption at levels up to one or more egg per day and risk of CHD in non-diabetic men and women.

Mutungi et al, 2008 (neutral quality) This was an RCT conducted in the US to compare the effects of a CHO-restricted diet high in cholesterol (provided by eggs) to one low in cholesterol (provided by egg substitutes) on the variables of metabolic syndrome. The CHO-restricted diet was composed of 10-15% of energy as CHO, 25-30% as protein (PRO), and 55-60% as fat and energy intake was not restricted. Subjects received weekly follow-up counseling and education and body mass and compliance were measured at visits. Three-day food records were obtained at baseline and five-day food records were completed during weeks one, six and 12. 31 males, age 40-70 years old, enrolled in the study; 28 completed the 12-week trial. Energy intake decreased in both groups from 10,243±4,040 to 7,968±2,401kJ (P<0.05) compared with baseline, and all subjects had reduced body weight and waist circumference (WC) (P<0.0001). The plasma TG concentration was reduced from 1.34±0.66 to 0.83±0.30mmol/L after 12 weeks (P<0.001) in all subjects. The plasma HDL-C concentration increased in the egg consumption group from 1.23±0.39 to 1.47±0.38mmol/L (P<0.01), whereas HDL-C did not change in the egg substitute consumption group; however, the plasma LDL-C concentration, as well as the LDL-C:HDL-C ratio, did not change during the intervention.

Nakamura et al, 2006 (neutral quality) This was a prospective cohort study conducted in Japan to examine the association between egg consumption and TC concentration, and CHD incidence. Two cohorts were analyzed: Cohort I, composed of 54,350 residents in four specific prefectures of Japan, aged 40-59 in 1990, and cohort II, composed of 62,288 residents in five specific prefectures of Japan, aged 40-69 in 1993-1994. Egg consumption was assessed through FFQs and subjects were followed through December 2001. Egg consumption was not associated with the risk of CHD, although TC was significantly related to the risk of CHD; the multivariate hazard ratio (HR) of CHD in subjects with TC >2,400 vs. <1,800mg/L was 2.17 (95% CI: 1.22, 3.85, P for trend=0.0018).

Qureshi et al, 2007 (positive quality) This was a prospective cohort study conducted in the US to study the association between egg intake and 20-year risk of CVD and mortality in subjects from the NHANES-I Epidemiologic Follow-up Study (NHEFS). Egg consumption was categorized into no or less than one egg, one to six eggs or greater than six eggs per week, during four follow-up periods in 1982-1984, 1986, 1987 and 1992. A total of 9,734 adults (3,756 males, 5,978 females, aged 25-74 years at the time of the original study) were included in the analysis. After adjusting for several factors, no relationship was observed between consuming more than six eggs per week and risk of stroke (RR=0.9, 95% CI: 0.7-1.1); there was also no relationship between more than six eggs per week and risk of ischemic stroke (RR = 0.9, 95% CI: 0.7-1.1). Subjects with higher egg intake had NS difference than lower intake groups in RR for risk of MI (RR=1.0, 95% CI: 0.9-1.3) or all-cause mortality (RR=1.0, 95% CI: 0.9-1.1). There was an increased risk for MI in some of the diabetic subjects who consumed more than six eggs per week (RR=2.0, 95% CI: 1.0-3.8), however, this same risk was not observed for either type of stroke.

Reaven et al, 2001 (neutral quality) This was an RCT of post-menopausal women to test the effects of increasing levels of dietary cholesterol intake on TC and LDL-C. Subjects were 65 healthy, post-menopausal women, 31 defined as insulin resistant (IR) and 34 as insulin sensitive (IS). Subjects were studied over a 12-week period: Four weeks of low-cholesterol baseline, four-week washout, and four weeks on 319mg, 523mg or 941mg cholesterol per day. The designated amount of cholesterol was obtained from eggs. The changes in TC and LDL-C in response to increments in dietary cholesterol up to the highest dose were not statistically significant and there were no differences between the IS and IR groups.

Tanasescu et al, 2004 (positive quality) This was a prospective cohort study, using a sub-population from the Nurses' Health Study, conducted in the US to assess the relationship between different types of dietary fat and cholesterol and the risk of CVD among women with T2D. The Nurses' Health Study started in 1986 with follow-up questionnaires sent every two years until 1996. Dietary fat and cholesterol were assessed through semiquantitative FFQs. A total of 5,672 female nurses (between the ages of 30-55 years in 1976) had reported a physician's diagnosis of diabetes at age >30 years on any follow-up questionnaire and were included in the analysis. Between 1980 and 1998, 619 new cases of CVD (non-fatal MI, fatal CHD and stroke) were identified. The RR of CVD for an increase of 200mg cholesterol per 1,000kcal was 1.37 (95% CI: 1.12-1.68, P=0.003). Each 5% of energy intake from SFA, as compared with equivalent energy from CHO, was associated with a 29% greater risk of CVD (RR=1.29, 95% CI: 1.02-1.63, P=0.04). The P:S ratio (polyunsaturated fat (PUFA) to SFA) was inversely associated with the risk of fatal CVD. Replacement of 5% of energy from SFA with equivalent energy from CHO or monounsaturated fat (MUFA) was associated with a 22% or 37% lower risk of CVD, respectively.

Tannock et al, 2005 (neutral quality) This was a randomized crossover trial to examine the effects of dietary cholesterol on markers of inflammation in 201 subjects divided into three a priori defined groups: Lean insulin-sensitive (LIS), N=66; lean insulin-resistant (LIR), N=78; and obese insulin resistant (OIR), N=59. For this analysis, subjects ingested zero or four eggs per day for four weeks in random order, with a background NCEP Step 1 diet (monitored by three-day food records) and four-week washout. Egg feeding was associated with significant increases in both CRP and serum amyloid A (SAA) in the LIS group (both P<0.01) but not in the LIR or OIR groups, although CRP and SAA were significantly higher in the latter two groups at baseline. Egg feeding was associated with a significant increase in HDL-C for all three groups. Egg feeding also was associated with a significant increase in non-HDL-C in LIS subjects (P<0.01); however, there was no correlation between the changes in non-HDL-C or changes in either CRP or SAA in this group. Circulating cytokines (IL-1b, IL-6, IL-8 and TNF-a) were not increased with egg feeding in any groups. Overall, a limitation of this analysis is that it is based on the same study population as that of Knopp et al; however, the outcomes and conclusions regarding egg consumption are different and more general measures are provided (e.g., there is no measure of LDL-C, only non-HDL-C).

Weggemans et al, 2001 (positive quality) This was a meta-analysis to examine the effects of dietary cholesterol on the ratio of total to HDL-C. Studies were identified in MEDLINE and Biological Abstracts searches (1974-1999). Of 222 studies identified, 17 studies with 556 subjects met the inclusion criteria. The meta-analysis included men and women with a wide age range from North America, Europe and South Africa. The analysis showed that addition of 100 mg cholesterol per day increased the ratio of TC to HDL-C by 0.02 units (95% CI: 0.01-0.03); TC by 2.2mg/dL (95% CI: 1.8-2.5mg/dL); and HDL-C by 0.3mg/dL (95% CI: 0.2-0.4mg/dL). However, when subjects were divided into two sub-groups based on PUFA and SFA intake (PUFA:SFA <0.7 or >0.7), the association between dietary cholesterol and increased serum LDL-C was attenuated in the low SFA group, with a statistically significant difference between high and low SFA groups.

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Author, Year, Study Design, Class, Rating	**Study Description and Duration**	**Study Population, Demographics and Location**	**Intervention Protocol**	**Significant Outcomes**	**Limitations**
Ballesteros et al 2004 Study Design: Randomized Crossover Trial Class: A Rating:	30-day intervention followed by a three-week washout period, followed by the opposite intervention for 30 days.	N=60 children [30 boys (aged 10.6±1.6 years) and 30 girls (aged 10.2±1.5 years)] enrolled. N=54 children (25 boys, 29 girls) completed the trial. Location: Mexico.	Children were divided into two groups and randomly assigned to either egg or egg substitute intervention for 30 days followed by a three-week washout period, followed by the opposite intervention for 30 days. Children consumed either two whole eggs (providing 518mg additional dietary cholesterol) or the equivalent amount of egg whites with added color, served scrambled for breakfast in the school cafeteria. On weekends, eggs and egg	Children were classified as hyporesponders (N=36), defined as no ↑ or <0.05mmol/L ↑ in plasma cholesterol for 100mg cholesterol or hyperresponders (N=18), defined as an ↑ of >0.06mmol/L in plasma cholesterol for 100mg cholesterol. During egg	Sponsored by the American Egg Board.

			substitute were packed for consumption and parents were instructed on proper administration.	During egg consumption period, hyperresponders had an ↑ of both LDL-C (from 1.54±0.38 to 1.93±0.36mmol/L) and HDL-C (from 1.23±0.26 to 1.35±0.29mmol/L), while hyporesponders had NS alterations in plasma LDL-C or HDL-C. All subjects, however, had an ↑ in LDL peak diameter ($P<0.01$) and a ↓ in the smaller LDL sub-fractions ($P<0.01$) during the egg consumption period.	
Djousse et al 2008 Study Design: Prospective Cohort Study Class: B Rating:	Physicians' Health Study. Average follow-up of 20 years.	21,327 American male physicians. Mean age: 53.7±9.5 years, range 40-85 years. Location: United States.	Examined association between egg consumption and risk of CVD and mortality. Information on egg consumption obtained at baseline, 24, 48, 72, 96 and 120 months using a semi-quantitative FFQ.	After an average follow-up of 20 years, a total of 1,550 new MI, 1,342 incident strokes and 5,169 deaths occurred in the cohort. Egg consumption not associated with incident MI, total stroke or types of stroke. While egg consumption of up to six eggs per week was not associated with risk of all-cause mortality, consumption of ≥seven eggs per week was associated with a 23% ↑ risk of death after controlling for confounders (P for trend <0.0001). In addition, compared with lowest category of egg consumption, intake of ≥seven per week was associated with 22% ↑ risk of death in the absence of prevalent diabetes, whereas a two-fold ↑ risk of death was observed in the presence of prevalent diabetes (P for interaction between diabetes	Study substituted missing values at baseline using reported egg consumption at 24 months in 113 individuals. Lack of detailed dietary data prevented adjustment for energy and other major nutrients. Sample consisting of male physicians limits generalizability of the findings. Unable to examine the effects of SFA, markers of insulin resistance, lipid and other nutrients or relevant biomarkers on the observed positive association in diabetic subjects.

				and egg consumption was 0.029 in the parsimonious model and 0.09 in the multivariable adjusted model).	
Goodrow et al 2006 Study Design: Randomized Crossover Trial Class: A Rating:	Duration: 18 weeks.	N=33 older adults [seven men (mean age 77±4 years) and 26 women (mean age 81±2 years)] enrolled and completed the trial. Location: United States.	The 18-week trial consisted of four phases: Phase I (baseline period; participants instructed to limit consumption of foods ↑ in lutein and zeaxanthin and avoid eggs or ↑-egg content foods) Phase II (five-week intervention; subjects consumed either no egg or egg substitute or one egg per day in addition to their normal diet) Phase III (four-week washout period similar to phase I) Phase IV (five-week crossover intervention from phase II). A seven-day diet record obtained from each subject during each phase of the study.	After egg consumption period, serum lutein ↑ by 26% and serum zeaxanthin ↑ by 38% (both P<0.001), while serum concentrations of TC, LDL-C, HDL-C and TG were not affected.	Sample size was relatively small, most subjects were female and the age range was very broad. Sponsored by the American Egg Board.
Greene CM et al 2005 Study Design: Randomized Crossover Trial Class: A Rating:	Two 30-day intervention periods separated by a three-week washout period.	N=42 older adults (13 men >60 years of age, 29 postmenopausal women) enrolled and completed the trial. Age not specified. Location: United States	Subjects assigned to either equivalent of three eggs per day (containing ~640mg dietary cholesterol) or same volume of egg substitute for 30 days, followed by a three week washout period, and then assigned to opposite intervention for 30 days. Seven-day dietary record collected during each period.	In both men and women, TC (P<0.05), LDL-C (P<0.05), HDL-C (P<0.001) and LDL particle size (P<0.05) ↑ during the egg consumption period. However, no differences between egg and egg substitute consumption periods with regard to LDL:HDL ratio, plasma tTG, apo-B concentration and parameters of LDL oxidation.	Relatively small sample size, predominantly composed of females; subjects not well described. Significant differences in WC and HDL-C concentrations between men and women at baseline. Sponsored by the American Egg Board/Egg Nutrition Center.
Harman et al 2008 Study Design: Randomized Controlled Trial Class: A Rating:	Duration: 12 weeks.	N=53 subjects randomly assigned. N=45 subjects completed trial: • N=24 in group consuming eggs (eight male, 17 female, mean age 44.9±8.4 years) • N=21 in control group (six male, 15 female, mean age 43.0±10.5 years).	Subjects were randomly assigned to one of two parallel dietary interventions: 1) An energy restricted diet (↓ by 500-1,000kcal per day) which included two eggs (N=27) 2) No eggs (N=26) per day for 12 weeks. All subjects received dietetic counseling and individualized	Energy intake ↓ by 25 and 29% in the egg-fed and non-egg-fed groups, resulting in a moderate weight ↓ of 3.4kg (P<0.05) and 4.4kg (P<0.05), respectively. Concentration of plasma LDL-C ↓ in the non-egg-fed	Study was not sufficiently controlled or statistically powered. Supported by the British Egg Industry Council.

		Location: United Kingdom.	diet plan and weight loss monitored through regular meetings with a dietitian. Seven-day food diary completed at baseline and after six weeks.	group after six weeks (P<0.01) and in the egg-fed and non-egg-fed at 12 weeks relative to baseline, however, no other significant Δ in plasma lipoproteins or LDL particle size.	
Hu FB, Stampfer MJ et al, 1999 Study Design: Prospective Cohort Study Class: B Rating:	Analysis of: 1) Health Professionals Follow-up Study (HPFS); eight-year follow-up 2) Nurses Health Study (NHS); 14-year follow-up.	N=37,851 men (aged 40-75 years). N=80,082 women (aged 34-59 years).	Followed for incident non-fatal MI, fatal CHD and stroke. Egg intake determined with FFQ.	N=866 cases of CHD and 258 cases of stroke in men in eight-year follow-up. RR of CHD across categories of intake was 1.08 (P for trend =0.75) for highest egg consumption group (> one egg per day) for men. N=939 cases of CHD and 563 cases of stroke in women during the 14-year follow-up. RR of CHD across categories of intake was 0.82 (P for trend =0.95) for highest egg consumption group for women. After adjustment for age and other CHD risk factors, NS association between egg consumption and risk of CHD or stroke in men or women. In subjects with T2D, positive association between egg intake and CHD risk (RR=2.02, P for trend=0.04, for men and RR=1.49, P for trend=0.008, for women).	None.
Knopp RH, Retzlaff B et al, 2003 Study Design: Randomized Controlled Trial Class: A Rating:	Double-blinded, randomized, three-period crossover clinical trial with three four-week intervention periods with four-week washout.	Subjects divided based on BMI and insulin sensitivity to three groups: N=65 Insulin sensitive (IS) N=75 Insulin resistant (IR) N=58 Obese, insulin-resistant (OIR).	Consumption of zero, two or four eggs per day. Background NCEP Step 1 diet (monitored by three-day food records).	Consumption of four eggs per day associated with ↑ LDL-C in IS (7.8%) and IR (3.3%) groups (both P<0.05), but not OIR group (NS). HDL-C levels ↑ significantly in all groups: 8.8%, 5.2% and 3.6% in IS, IR and OIR groups, respectively, with	None.

				consumption of four eggs per day. Significantly ↓ TG (-5.5%) with consumption of four eggs per day in IS group.	
Kritchevsky SB and Kritchevsky D, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating:	Summary of epidemiological evidence relating dietary cholesterol and egg intake to CVD.	N=8 prospective cohort studies relating dietary cholesterol and risk of CVD. N=6 prospective cohort studies relating egg consumption and risk of CVD.	Dietary cholesterol. Egg cholesterol.	Association between dietary cholesterol and heart disease risk is small. 6% ↑ CVD risk for 200mg per 1,000kcal per day difference in cholesterol intake. No association between egg consumption at >one egg per day and risk of CVD in non-diabetic men and women.	None.
McNamara DJ, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating:	Pooled quantitative analysis.	N=167 articles on cholesterol feeding studies in 3,519 subjects. 1960-2000. Studies limited to cross-over design with cholesterol intake sole variable.	Studies used dietary cholesterol concentrations from ↑ (100-300mg per day) to ↓ (3-5g per day) intakes adjusted for body weight to 70kg and plasma cholesterol to 100mg per day Δ.	Plasma cholesterol ↑ by 2.2mg/dL for 100mg per day cholesterol intake. Hyper-responders: Plasma cholesterol ↑ by 3.9mg/dL for 100mg per day. Hypo-responders: Plasma cholesterol ↑ by 1.4mg/dL for 100mg per day. NS Δ in LDL:HDL ratio (2.60 to 2.61).	None.
Mutungi et al 2008 Study Design: Randomized Controlled Trial Class: A Rating:	Duration: 12 weeks.	N=31 males enrolled. N=28 completed the trial. Age: 40-70 years. Location: United States.	Compared effects of a CHO-restricted diet ↑ in cholesterol (provided by eggs) to one ↓ in cholesterol (provided by egg substitutes) on the variables of metabolic syndrome. CHO-restricted diet composed of 10-15% of energy as CHO, 25-30% as PRO and 55-60% as fat; energy intake not restricted. Subjects received weekly follow-up counseling and education and body mass and compliance measured at visits. Three-day food records obtained at baseline and five-day food records completed during weeks one, six and 12.	Energy intake ↓ in both groups from 10,243±4,040 to 7,968±2,401kJ (P<0.05) compared with baseline, and all subjects had ↓ body weight and WC (P<0.0001). Plasma TG concentration was ↓ from 1.34±0.66 to 0.83±0.30mmol/L after 12 weeks (P<0.001) in all subjects. Plasma HDL-C concentration ↑ in egg consumption group from 1.23±0.39 to 1.47±0.38mmol/L (P<0.01), whereas HDL-C did not Δ in egg substitute	All male subjects and sample not well described; unclear if sample was representative. Sponsored by the Egg Nutrition Center.

				consumption group; however, no Δ in the plasma LDL-C concentration or LDL:HDL ratio.	
Nakamura et al 2006 Study Design: Prospective Cohort Study Class: B Rating:	Duration: Subjects followed through December 2001.	Two cohorts were analyzed: Cohort I, composed of 54,350 residents in four specific prefectures of Japan, aged 40-59 in 1990 Cohort II, composed of 62,288 residents in five specific prefectures of Japan, aged 40-69 in 1993-1994. Location: Japan.	Examined association between egg consumption and TC concentration and CHD incidence. Egg consumption assessed through FFQ.	Egg consumption was not associated with risk of CHD, although TC was significantly related to risk of CHD; the multivariate HR of CHD in subjects with TC >2,400 vs. <1,800mg/L was 2.17 (95% CI: 1.22, 3.85, P for trend=0.0018).	Egg consumption only measured at baseline and was measured in days per week rather than number of eggs per week. Portion sizes not specified, total energy intake could not be used as a covariate in the analyses. TC concentration was only available for some of the subjects.
Qureshi et al 2007 Study Design: Prospective Cohort Study Class: B Rating:	Duration: 20-year follow-up.	N=9,734 adults (3,756 males, 5,978 females) included in analysis, from the NHANES-I Epidemiologic Follow-up Study (NHEFS). Age: 25-74 years at time of original study. Location: United States.	Studied the association between egg intake and risk of CVD and mortality. Egg consumption was categorized into no or six eggs per week, during four follow-up periods in 1982-1984, 1986, 1987 and 1992.	After adjusting for several factors, no relationship observed between consuming >six eggs per week and risk of stroke (RR=0.9, 95% CI: 0.7-1.1); there was also no relationship between >six eggs per week and risk of ischemic stroke (RR=0.9, 95% CI: 0.7-1.1). Subjects with higher egg intake had NS difference than lower intake groups in RR for risk of MI (RR=1.0, 95% CI: 0.9-1.3) or all-cause mortality (RR=1.0, 95% CI: 0.9-1.1). ↑ risk for MI in some of the diabetic subjects who consumed >six eggs per week (RR=2.0, 95% CI: 1.0-3.8), however, this same risk not observed for either type of stroke.	None.
Reaven GM, Abbasi F et al, 2001 Study Design: Randomized Controlled Trial Class: A Rating:		N=65 healthy, postmenopausal women (31 insulin resistant, 34 insulin sensitive).	12-week trial: • Four weeks of low-cholesterol baseline • Four-week washout • Four weeks on 319mg, 523mg, or 941mg cholesterol per day. Cholesterol was from eggs.	Δ in TC and LDL-C in response to increments in dietary cholesterol up to the highest dose were not statistically significant. No differences between IS and IR groups.	None.
Tanasescu et al 2004 Study Design: Prospective Cohort Study	Nurses' Health Study. Duration: 18-year follow-up.	N=5,672 female nurses who reported a physician's diagnosis of diabetes at age >30 years on any follow-up questionnaire. Age: 30-55 years in 1976.	Assessed relationship between different types of dietary fat and cholesterol and risk of CVD among women with T2D. Nurses' Health Study started in 1986 with follow-up	Between 1980 and 1998, 619 new cases of CVD (nonfatal MI, fatal CHD and stroke) were identified. RR of CVD for an ↑	Assessment of MUFA was difficult due to shared food sources of SFA and MUFA.

Class: B Rating:		Location: United States.	questionnaires sent every two years until 1996. Dietary fat and cholesterol assessed through semi-quantitative FFQ.	of 200mg cholesterol per 1,000kcal was 1.37 (95% CI: 1.12-1.68, P=0.003). Each 5% of energy intake from SFA, as compared with equivalent energy from CHO, was associated with a 29% ↑ risk of CVD (RR=1.29, 95% CI: 1.02-1.63, P=0.04). P:S ratio inversely associated with risk of fatal CVD. Replacement of 5% of energy from SFA with equivalent energy from CHO or MUFA was associated with a 22% or 37% ↓ risk of CVD, respectively.	
Tannock LR, O'Brien KD et al, 2005 Study Design: Randomized Controlled Trial Class: A Rating:		N=201 subjects divided into three defined groups: 1) N=66 Lean insulin-sensitive (LIS) 2) N=78 Lean insulin-resistant (LIR) 3) N=59 Obese insulin resistant (OIR).	Zero or four eggs per day for four weeks. Background NCEP Step 1 diet (monitored by three-day food records). Four-week washout.	Egg feeding associated with significant ↑ in CRP and SAA in LIS group (both P<0.01), but not in LIR or OIR groups. Egg feeding associated with significant ↑ in HDL-C for all three groups. Egg feeding associated with significant ↑ in non-HDL-C in LIS group (P<0.01). No correlation between Δ in non-HDL-C or Δ in CRP or SAA in LIS group. Circulating cytokines (IL-1b, IL-6, IL-8 and TNF-a) not ↑ with egg feeding in any groups.	None.
Weggemans RM, Zock PL et al, 2001 Study Design: Meta-analysis or Systematic Review	Studies identified in MEDLINE and Biological Abstracts (1974-1999).	Men and women with a wide age range from North America, Europe and South Africa. Location: International.	N=17 with 556 subjects met inclusion criteria (of 222 studies identified).	Addition of 100mg cholesterol per day: ↑ ratio of TC:HDL-C by 0.02 units (95% CI: 0.01-0.03) ↑ TC by 2.2mg/dL	None.

Class: M Rating:				(95% CI: 1.8-2.5mg/dL) ↑ HDL-C by 0.3mg/dL (95% CI: 0.2-0.4mg/dL). Association between dietary cholesterol and ↑ LDL-C attenuated in the ↓ SFA, vs. ↑ SFA, group (P=0.03).	

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

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